Inventor: Serial No.: 08/471,622

William D. Huse

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Figures 3A, 3B and 3C is the nucleotide sequence of M13IX11 (SEQ ID NO:2).

Figures 4A, 4B and 4C is the nucleotide sequence of M13IX34 (SEQ ID NO: 3).

Figures 5A, 5B and 5C is the nucleotide sequence of M13IX13 (SEQ ID NO: 4).

Figures 6A, 6B and 6C is the nucleotide sequence of M13IX60 (SEQ ID NO: 5).

On page 7, please delete lines 1 through 17 and substitute therefor:

Expression of heteromeric receptors such as antibodies or functional fragments thereof on the surface of M13 can be accomplished, for example, using the vector system shown in Figure 1. Construction of the vectors enabling one of ordinary skill to make them are explicitly set out in Example I. complete nucleotide sequences are given in Figures 2A, 2B and 2C and Figures 3A, 3B and 3C (SEQ ID NOS: 1 and 2). This system produces randomly combined populations of heavy (Hc) and light (Lc) chain antibody fragments functionally linked to expression elements. The Hc polypeptide is produced as a fusion protein with the M13 coat protein encoded by gene VIII. The gVIII-Hc fusion protein therefore anchors the assembled Hc and Lc polypeptides on the surface of M13. The diversity of Hc and Lc

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combinations obtained by this system can be 5×10^7 or greater. Diversity of less than 5×10^7 can also be obtained and will be determined by the need and type of heteromeric receptor to be expressed.

On page 26, please delete lines 16 through 31 and substitute therefor:

The third step in constructing M13IX30 involved inserting the expression and cloning sequences from M13IX04B upstream of the pseudo wild-type gVIII in M13IX01F. This was accomplished by digesting M13IX04B with Dra III and Bam HI and gel isolating the 700 base pair insert containing the sequences of interest. M13IX01F was likewise digested with Dra III and Bam HI. The insert was combined with the double digested vector at a molar ratio of 1:1 and ligated as described in Example I. The sequence of the final construct M13IX30, is shown in Figures 2A, 2B and 2C (SEQ ID NO: 1). Figure 1A also shows M13IX30 where each of the elements necessary for surface expression of Hc fragments is marked. It should be noted during modification of the vectors, certain sequences differed from the published sequence of M13mp18. The new sequences are incorporated into the sequences recorded herein.

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On page 29, please delete lines 17 through 21 and substitute therefor:

The sequence of the resultant vector, M13IX11, is shown in Figures 3A, 3B and 3C (SEQ ID NO: 2). Figure 1B also shows M13IX11 where each of the elements necessary for producing a surface expression library between Lc fragments is marked.

On page 39, please delete line 10 through page 40, line 10 and substitute therefor:

M13IX34 (SEQ ID NO: 3) was created from M13IX33 by cloning in the gene encoding a human IgG1 heavy chain. The reading frame of the variable region was changed and a stop codon was introduced to ensure that a functional polypeptide would not be produced. The oligonucleotide used for the mutagenesis of the variable region was 5'-CACCGGTTCGGGGAATTAGTCTTGACCAGGCAGCCCAGGGC-3' (SEQ ID NO: 72). The complete nucleotide sequence of this vector is shown in Figures 4A, 4B and 4C (SEQ ID NO: 3).

Several vectors of the M13IX11 series were also generated to contain similar modifications as that described for the vectors M13IX53 and M13IX34. The promoter region in M13IX11 was mutated to conform to the 35 consensus sequence to generate M13IX12. The oligonucleotide used for this mutgenesis was 5'-ATTCCACACATTATACGAGCCCGGAAGCATAAAGTGCAAGCCTGGGGTGCC-3' (SEQ ID NO: 73). A human kappa light chain sequence was cloned into M13IX12 and the variable region subsequently deleted to generate

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M13IX13 (SEQ ID NO: 4). The complete nucleotide sequence of this vector is shown in Figures 5A, 5B and 5C (SEQ ID NO: 4). A similar vector, designated M13IX14, was also generated in which the human lambda light chain was inserted into M13IX12 followed by deletion of the variable region. The oligonucleotides used for the variable region deletion of M13IX13 and M13IX14 were 5'-CTGCTCATCAGATGGCGGGAAGAGCTCGGCCATGGCTGGTTG-3' (SEQ ID NO: 74) and 5'-GAACAGAGT GACCGAGGGGGGGGGCGAGCTCGGCCATGGCTGGTTG-3' (SEQ ID NO: 75), respectively.

The Hc and Lc vectors or modified forms thereof can be combined using the methods described in Example I to produce a single vector similar to M13IX53 that allows the efficient incorporation of human Hc and Lc encoding sequences by mutagenesis. An example of such a vector is the combination of M13IX13 with M13IX34. The complete nucleotide sequence of this vector, M13IX60, is shown in Figures 6A, 6B and 6C (SEQ ID NO: 5).

In the claims:

Please amend the claims to read as follows:

1. (Amended) A composition of matter comprising a plurality of procaryotic cells containing diverse combinations of first and second DNA sequences encoding first and second polypeptides which form heteromeric receptors functional in the absence of its membrane attachment domain, said first and second